

REMARKS

Claims 1-9 and 11-28 currently appear in this application. The Office Action of October 21, 2002, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by any of U.S. Patents 5,496,545 or 6,083,495 or 5,667,775 to Holmes-Farley et al. (hereinafter Holmes).

This rejection is respectfully traversed. True specific gravity (true density) is defined as follows:

True specific gravity is the specific gravity of solid materials and can be calculated by dividing the weight of a solid material by the volume of the solid material which is measured under conditions such that volume of voids or pores in the solid material is excluded from the volume of the solid material.

In the present invention, true specific gravity was measured using a true specific gravity measuring apparatus, "Accupick Model 1330", Shimazu Seisakusho K.K., Japan, by means of the helium gas substitution method. According to this method, the volume of a solid material is measured under conditions as if the solid

material has no void or pore larger than that of the helium molecule. Specific gravity determined by this method is the same as true specific gravity or true density as explained above.

Submitted herewith are copies of Dittgen et al., *Manufacturing Chemist*, July, 1993, pages 17, 19, and 21 and Henck et al., *Journal of Pharmaceutical Sciences* **88(1)**: 1999, pages 103-107. These references are submitted in order to confirm what is meant by true specific gravity (or true density) of a chemical compound.

True specific gravity (true density) is broadly used as one parameter for identifying powdery or particulate solid materials. Particularly, true specific gravity in polymers represents their physical structure in the same way as their crystalline structure, molecular structure, etc. The difference in physical structure between a polymer of the present invention and a polymer of the prior art based upon true specific gravity typically affects the properties for forming tablets. That is, uncoated tablets formed from polymers which have different structures by virtue of their different true specific gravity, will have different properties.

In general, a polymer which has the same chemical structure as, but has a different true specific

gravity from another polymer exhibits different physical properties from the other polymer. Therefore, when these two polymers are formed into tablets, the properties of the tablets are different from each other.

Dittgen et al., submitted herewith, discussed tablets formed from microcrystalline cellulose, which is not the same polymer as in the present invention. However, as with polymers of the present invention, a microcrystalline cellulose having a certain true density different from another microcrystalline cellulose having a different true density exhibits different crystallinity, as shown in Figure 1 on page 17 and in the "results" in the left column on page 19.

In Henck et al., there is a discussion of polymorphism exemplified by Flurbiprofen. In the left column on page 107, it is noted that density (*i.e.*, true density) is a very important parameter for determining which one of two modifications is thermodynamically stable at absolute zero. This article also discloses that, according to the density rule, the modification with the lower density is thermodynamically unstable at absolute zero compared with the crystal form having a higher density.

It can be concluded from these two articles that a polymer or a compound having one true density is

different in physical structure or physical properties from another polymer having the same chemical structure but a different true density. The present invention also demonstrates that the phosphate-binding polymer of the present invention, which has a true density of from 1.18-1.24, exhibited different behavior in tableting properties from a polymer of Holmes which has a true density outside of the range of the present invention.

As stated in the specification as filed and in the declaration of Katsuya MATSUDA submitted herewith, a phosphate-containing polymer of the present invention can be prepared by crosslinking polyallylamine with epichlorohydrin in a mixed solvent of water and acetonitrile. If the solvent used in the crosslinking reaction is water alone, as in Holmes, the resulting polymer has a true density of more than 1.24, even though the chemical formula of the polymer is the same as that of the present invention.

The polymer of the present invention has unexpectedly good properties for preparing tablets. These unexpectedly good properties are described in the specification as filed at page 3, line 17 through page 5, line 21. These properties can be summarized as follows:

1. The tablets should substantially consist of a

phosphate-binding polymer in the absence of or at a minimum amount of additives such as microcrystalline cellulose or low substituted hydroxypropyl cellulose. Thus, the tablets to be made are relatively small.

2. The tablet is sufficiently hard to be coated with a coating film. The coating is critical in this type of tablet in order to prevent disintegration in the mouth and to provide improved ingestion of the contents.

Since the polymer of the present invention has different characteristics from the polymer of Holmes, it is respectfully submitted that the Holmes patents do not anticipate the herein claimed invention.

Claims 1-9 and 11-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of the Holmes patents discussed above.

The polymers of the present invention are crosslinked using a mixture of water and acetonitrile, while the Holmes polymers are crosslinked in the presence of only water. While the chemical structures of these polymers may be the same, their true specific gravities are different, resulting in polymers having different physical properties. As shown in the MATSUDA declaration submitted herewith, polymers crosslinked only in the presence of water had a specific gravity of 1.2530 to 1.2549. The polymers made by the process of the present

invention, however, in which the polymer was crosslinked in the presence of both water and acetonitrile, had specific gravities ranging from 1.2094 to 1.2089. When the polymers were compressed under static pressure to form tablets, the tablets obtained from polymers prepared according to the Holmes method exhibited compression pressure of 3.6 KP and 5.6 KP. It should be noted that a compression pressure of about 2000 kilograms is almost the acceptable upper limit for preparing tablets using a tableting machine.

In contrast thereto, the polymers of the present invention, having a true specific gravity of 1.209, 1.211 and 1.211, respectively, provided tablets having a hardness of 23.9 KP, 24.3 KP and 15.5 KP, respectively. This is shown in Table 1 on page 13 of the instant specification.

According to the method of Example 3 of the present application, tablets containing the polymers were prepared with a tableting machine at a compression pressure of 2000 kg or 900 kg. The polymer had a true specific gravity of 1.21 and a water content of 5.1%. The tablets prepared had a weight of 290 mg/tablet, a diameter of 9.5 mm, and contained 250 mg of the polymer per tablet on a dry basis.

In re Appl. No. 09/807,190  
Confirmation No. 4190

The thus prepared tablets were subjected to a test for measuring the maximum weight loss according to The United States Pharmacopoeia (USP) 24, The National Formulary (NF) 19, No. 1216-Tablet Friability. The tests were conducted at 25 rpm for 30 minutes.

Table III shows the test results for an average of 20 tablets:

Table III

Lot	Compression Pressure (kg)	Hardness (KP)	Weight Loss (%)
F-1	2,000	16.7	0.85
F-1B	900	5.0	4.23

It is clear from the results shown in Table III that the tablet having a hardness of 5KP showed a weight loss of 4.23%, which is not deemed to be desirable for coating processes. The tablet having a hardness of 16.7 KP, however, was deemed to be desirable for coating.

When the uncoated tablets described in Table III were subjected to film coating, the tablets having a hardness of 5 KP exhibited a remarkable weight loss on the surface thereof at the beginnings stage of the coating step, thereby producing a significantly rough surface on the coated tablet. On the other hand, the tablets having a hardness of 16.7 KP produced coated tablets having a smooth surface.

Thus, it is clear that polymers having a density in the range claimed herein are unexpectedly

In re Appl. No. 09/807,190  
Confirmation No. 4190

superior for forming tablets to the polymers disclosed in  
Holmes.

In view of the above, it is respectfully  
submitted that the claims are now in condition for  
allowance, and favorable action thereon is earnestly  
solicited.

Respectfully submitted,

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